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Open study evaluating lamotrigine efficacy and safety in add-on treatment and consecutive monotherapy in patients with carbamazepine- or valproate-resistant epilepsy

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Lamotrigine is a broad-spectrum antiepileptic drug that blocks sodium channels, thereby inhibiting the pre-synaptic release of excitatory neurotransmitters. The primary aim of the study was to evaluate lamotrigine add-on therapy and consecutive monotherapy in patients with epilepsy whose seizures were not controlled by carbamazepine or valproate. One hundred and twenty six epilepsy patients at 18 centres in Poland were recruited into a lamotrigine substitution study. In all patients, existing seizures were poorly controlled with valproate ($n = 63$) or carbamazepine ($n = 63$) monotherapy. The study consisted of four phases: (1) a 4-week lamotrigine dose-escalation phase, (2) an 8-week lamotrigine add-on phase, (3) an 8-week carbamazepine/valproate withdrawal phase, and (4) an 8-week lamotrigine monotherapy phase.

Of 126 patients recruited into the study, 107 (85%) completed dose-escalation and add-on therapy with lamotrigine and 85 (68%) completed lamotrigine monotherapy. Fifty percent of patients during add-on therapy and 53% during lamotrigine monotherapy experienced at least 50% reduction in total seizures (responders) compared to the pre-study period. Approximately 20% of patients during add-on therapy and 27% during lamotrigine monotherapy were seizure free. Total well-being was assessed using a Visual Analogue Scale with 62% of patients during add-on therapy and 60% in lamotrigine monotherapy reporting improvement in scores. Lamotrigine was generally well tolerated. Treatment was discontinued in 7% because of adverse events.

In conclusion, lamotrigine is an effective AED in add-on therapy and monotherapy, it is safe and well tolerated, and successful conversion from add-on to monotherapy can be achieved in many cases. An additive effect between lamotrigine and valproate was observed.

Key words: lamotrigine; add-on; monotherapy; substitution study; adolescents; adults.

INTRODUCTION

Lamotrigine (LTG) is a novel anticonvulsant that inhibits the release of glutamate through blockade of voltage-sensitive sodium channels and through stabilization of the neuronal membrane[1]. However, this mechanism alone does not explain the broad clinical effica y of LTG. It has been suggested that inhibition of pre-synaptic N-type Ca^{2+} channels may contribute to its anticonvulsant effects[2].

Approximately 110 worldwide clinical trials involving almost 4000 adults have been completed in which LTG has been added to existing therapy or has been administered as monotherapy[3]. These trials have demonstrated the effica y of LTG against a wide range of seizure types in both adults and children and its effectiveness as add-on therapy for uncontrolled partial and generalized seizures has been established in many studies[4–8]. LTG has also been shown to be well tolerated[9,10]. Results of monotherapy studies suggested that LTG is at least as effective as carbamazepine, valproate or phenytoin monotherapy and is significantl better tolerated[11–13].

This open study was conducted to examine the effi cacy and safety of LTG as add-on therapy and consecutive monotherapy in adolescents (≥12 years of age)

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and adults whose seizures were not adequately controlled by carbamazepine or valproate.

MATERIALS AND METHODS

Patients

Seizures were classifie according to the International Classificatio of Epileptic Seizures. Adolescents (≥12 years) and adult patients were recruited to the study if they: (1) had a diagnosis of epilepsy uncomplicated by pseudoseizures; (2) had at least two seizures in the past 8 weeks; (3) were receiving carbamazepine or valproate in the past 8 weeks; (4) had stable treatment with one antiepileptic drug (AED) for at least 4 weeks before entering the study (at least 800 mg of carbamazepine daily in adults and 10 mg kg^{-1} in adolescents or at least 1000 mg of valproate daily in adults and 30 mg kg^{-1} in adolescents). All patients provided written informed consent.

Exclusion criteria were pregnancy or exposure to the risk of pregnancy, breastfeeding, clinically significan impairment of renal or hepatic function, or treatment with other medication which in the investigator's opinion contraindicated entry into the study. Treatment with oral contraceptives was acceptable.

Study design

The trial was approved by the local research ethics committee and by the Regulatory Authorities. It was conducted according to GCP rules and to the principles of the Declaration of Helsinki.

This was a multi-centre, open, prospective, parallel-group study conducted in four phases (Fig. 1). All prospective patients underwent a screening assessment. During the firs phase (weeks 1–4), LTG was added to the patients' existing anticonvulsant medication. In patients taking carbamazepine, doses of LTG were escalated from 50 mg per day (weeks 1 and 2) to 100 mg per day (weeks 3 and 4), whilst patients taking valproate received LTG 25 mg on alternate days (weeks 1 and 2) which was then increased to 25 mg per day (weeks 3 and 4).

During the second or 'add-on' phase (weeks 5–12), patients were maintained on both LTG and their original medication (carbamazepine or valproate). In patients receiving carbamazepine, the dose of LTG was adjusted to a target dose of 200–500 mg per day. In patients receiving valproate, LTG doses were continually escalated (50–75 mg per day, weeks 5 and 6; 100 mg per day, week 7; 150 mg per day, week 8), reaching 200 mg per day in weeks 9–12.

Phase 3 (weeks 13–20) consisted of a withdrawal period, during which patients' original medication was progressively reduced to achieve LTG monotherapy. At week 12 the patient was assessed to ensure that withdrawal of the concomitant standard AED and the change to LTG monotherapy was appropriate. The decision was based on treatment effica y (change in seizure frequency) and a physician's global evaluation. In patients taking valproate, doses of LTG were increased to 200–300 mg per day (at week 17) as valproate was withdrawn. In the fina study phase (weeks 20–28), all patients received LTG 200–500 mg per day monotherapy.

Patients also assessed their total well-being every 4 weeks during the study using a Visual Analogue Scale (VAS). The patient was asked to select a point on the scale according to their total well-being during the assessment period. The scale ranged from 0 (poor) to 10 (good). No supplementary information was supplied to patients about what they should include in their estimation.

Outcome measures and statistical analyses

The principal measure of effica y was the number of patients who experienced at least 50% reduction in seizure frequency during the add-on and monotherapy phases. For each study phase the mean seizure frequency is presented with 95% confidenc intervals (CIs). Comparison of mean seizure frequency between study phases was performed using Student's *t*-test for dependent samples. Comparison of treatment groups within each study phase was performed using a chi-squared test. The number of patients who completed the add-on phase and the monotherapy phase was also calculated.

Mean VAS scores for each treatment period are presented with 95% CIs. Comparison of VAS scores between treatment groups for each study phase was performed using a chi-squared test. Comparison of VAS scores between study phases for each treatment arm was performed using Student's *t*-test for dependent samples. The incidence and nature of adverse events and their relationship to LTG were recorded.

RESULTS

A total of 126 patients entered the study, 63 who were taking carbamazepine at baseline and 63 who were taking valproate. There were no differences between the treatment groups in terms of gender, age, weight or seizure type (Table 1).

There was no difference in the distribution of patients with different seizure types between the carbamazepine and valproate treatment groups (Table 2).

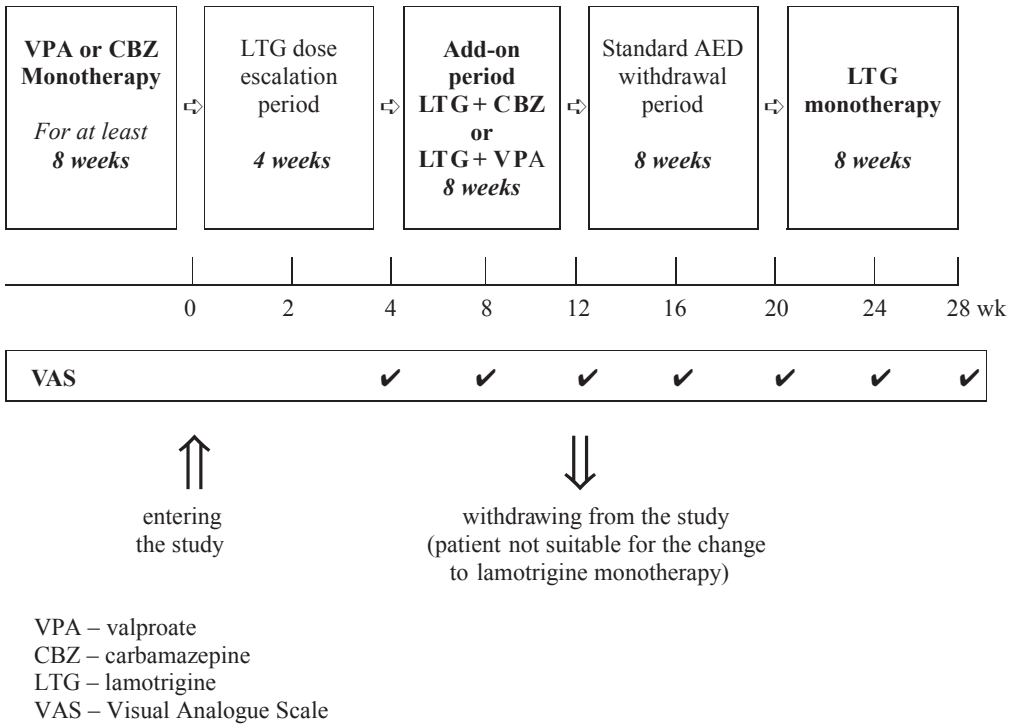

Fig. 1: Study design.

Table 1: Characteristics of patients at entry.

	Carbamazepine group $n = 63$	Valproate group $n = 63$	Total $n = 126$
Male/female (%)	54/46	51/49	52/48
Age (yr)			
Median (range)	25 (12–52)	19 (12–52)	23.5 (12–52)
Weight (kg)			
Median (range)	65 (31–95)	63 (25–105)	64 (25–105)
Seizures from (yr)			
Median (range)	10 (1–46)	7 (1–39)	8 (1–46)
Number of seizures in last 8 weeks			
Median (range)	8 (2–365)	8 (2–140)	8 (2–365)
Seizure type [*n* (%)]			
Partial seizures with or without secondary generalization	40 (64%)	37(59%)	77(61%)
Primary generalized seizures	22 (35%)	26 (41%)	48(38%)
Non-classifie	1 (1%)	0 (0%)	1 (1%)

In most patients the aetiology of the seizure was unknown ($n = 64, 51\%$). However in other patients there was a history of head trauma ($n = 26, 20\%$), birth trauma ($n = 10, 8\%$), CNS infection ($n = 10, 8\%$), cerebrovascular disorder ($n = 4, 3\%$) and brain tumour ($n = 1$).

Efficacy

Eighty-f ve out of 126 patients (67.5%) completed the transition from carbamazepine or valproate monotherapy through add-on treatment to LTG monotherapy. In the valproate treatment group, 51 out of 63 patients (81.0%) successfully transferred to LTG monotherapy whilst in the carbamazepine group, 34 out of 63 (53.1%) were well maintained on LTG monotherapy ($P = 0.001$, valproate vs. carbamazepine).

Seizure rates

Add-on period. During the add-on period, 63 out of 126 patients (50.0%) experienced at least 50% reduction in total seizures when compared to the 8-week period prior to commencing the study (Table 3). These patients are classifie as 'responders'. In the valproate treatment group, 37 out of 63 patients (58.7%) were re-

Table 2: Seizure type in observed population.

Seizure type	CBZ group (n)	VPA group (n)	Total (n)
Simple partial seizures	9	10	19
Complex partial seizures	23	21	44
Partial seizures with secondary generalization	18	23	42
Absence seizures	6	15	21
Myoclonic seizures	5	6	11
Clonic seizures	2	1	3
Tonic seizures	3	1	4
Tonic–clonic seizures	21	23	44
Atonic seizures	1	2	3
Non-classifie seizures	1	0	1

CBZ, carbamazepine; VPA, valproate.

sponders whilst in the carbamazepine treatment group 26 out of 63 patients (41.3%) were classifie as responders ($P = 0.05$: valproate responders vs. carbamazepine responders).

There was no statistical difference between the number of responders who reported primary generalized seizures at baseline (52.1%) and the responders who reported partial seizures with or without secondary generalization (48.1%).

Twenty f ve patients (19.8%) became seizure free during the LTG add-on period. The majority were receiving valproate at baseline (19 out of 63, 30.2%) with significantl fewer patients who were receiving carbamazepine at baseline achieving seizure-free status (6 out of 63, 9.5%; $P < 0.01$ between treatment groups).

In the valproate treatment group, mean seizure frequency was reduced from 19.1 (95% CI: 12.6; 25.7) during the 8-week period prior to entering the study to 8.6 (95% CI: 3.3; 13.9) during the 8-week add-on phase ($P < 0.001$, LTG and valproate vs. valproate monotherapy, $n = 57$). Similarly, mean seizure frequency was reduced from 25.6 (95% CI: 8.2; 43.0) to 18.3 (95% CI: 1.6; 35.0) in the carbamazepine group ($n = 50$) over the same period.

Monotherapy period. During the monotherapy period, 67 out of 126 patients (53.2%) were classifie as responders with a >50% reduction in seizure frequency (Table 3). In the valproate treatment group, 40 out of 63 patients (63.5%) were responders during the LTG monotherapy phase whilst 27 out of 63 of the carbamazepine group (42.9%) were responders ($P < 0.05$ between treatment groups).

Thirty four out of 126 patients (27.0%) were seizure free during LTG monotherapy, including 20 out of 63 (31.7%) in the valproate treatment group and 14 out of 63 (22.2%) in the carbamazepine group.

Seizure frequency was also reduced during the monotherapy phase. In the valproate treatment group, mean seizure frequency was reduced from 16.8 (95% CI: 11.6; 22.0) during the 8-week period prior to entering the study to 10.5 (95% CI: −2.5; 23.6) during the 8-week monotherapy phase ($n = 51$). Similarly, mean seizure frequency was reduced from 20.3 (95% CI: 5.8; 34.8) to 3.9 (95% CI: 1.9; 5.8) in the carbamazepine group ($P < 0.05$, LTG monotherapy vs. carbamazepine monotherapy; $n = 34$) over the same period.

Visual analogue scale

Add-on period. VAS scores were improved in 78 out of 126 patients (61.9%) between week 4 and week 12 indicating improved well-being. In 36 of these patients the improvement was >50% and in 42 patients the improvement was <50% (Table 4). In the valproate treatment group, 43 out of 63 patients (68.3%) showed improved scores whilst 35 out of 63 (55.6%) patients in the carbamazepine group showed improved scores.

In the valproate group ($n = 57$), VAS scores increased from 4.5 (95% CI: 4.0; 5.1) at week 4 to 6.3 (95% CI: 5.7; 6.9) at week 12 ($P < 0.001$). Similarly, scores increased from 5.6 (95% CI: 4.8; 6.3) to 6.5 (95% CI: 5.8; 7.1) in the carbamazepine group ($n = 50$) over the same period ($P = 0.015$).

Monotherapy period. Seventy f ve out of 126 patients (59.5%) showed improved VAS scores between week 4 and week 28. In 43 of these patients the improvement was >50% and in 32 patients the improvement was <50% (Table 4). In the valproate treatment group, 47 out of 63 patients (74.6%) showed improved scores whilst 28 out of 63 (44.4%) patients in the carbamazepine group showed improved scores.

Mean VAS scores increased throughout the duration of the study. The observed differences were statistically significan in both treatment groups (Table 5).

Safety

Forty nine out of 126 patients (38.9%) reported adverse events, including 22 out of 63 patients from the valproate treatment group (34.9%) and 27 out of 63 patients from the carbamazepine treatment group (42.9%). Adverse events were more frequent during the add-on period (41 out of 49, 83.7%) than during monotherapy. The most frequent adverse events were respiratory tract infection ($n = 11$, 8.7%) and dizziness ($n = 8$, 6.4%). Other adverse events noted were headache ($n = 7$, 5.6%), diplopia ($n = 5$, 4.0%), tremor ($n = 5$, 4.0%), somnolence ($n = 4$, 3.2%), insomnia ($n = 4$, 3.2%), nausea ($n = 4$, 3.2%) and asthenia ($n = 3$, 2.4%).

Table 3: Changes in seizure frequency—number of patients in each subgroup according to the percentage change in seizure frequency.

	LTG add-on therapy vs. CBZ/VPA monotherapy			LTG monotherapy vs. CBZ/VPA monotherapy		
	CBZ	VPA	All	CBZ	VPA	All
Seizure free (100%)	6	19	25	14	20	34
Reduction: >50% to <100%	20	18	38	13	20	33
Reduction: >0% to ≤50%	13	17	30	5	7	12
No change	2	1	3	0	0	0
Increase: >0% to ≤50%	3	1	4	2	2	4
Increase: >50%	6	1	7	0	2	2
Total	50	57	107	34	51	85

CBZ, carbamazepine; VPA, valproate.

Table 4: Changes in VAS scores—number of patients in subgroups according to the percentage change in VAS.

	Add-on therapy (week 12) vs. Escalation period (week 4)			LTG monotherapy (week 28) vs. Escalation period (week 4)		
	CBZ	VPA	All	CBZ	VPA	All
Improvement ≥100%	9	17	26	7	19	26
Improvement >50% to <100%	4	6	10	5	12	17
Improvement >0% to ≤50%	22	20	42	16	16	32
No change	2	1	3	1	1	2
Deterioration >0% to ≤50%	11	11	22	4	3	7
Deterioration >50%	2	2	4	1	0	1
Total	50	57	107	34	51	85

CBZ, Carbamazepine; VPA, Valproate; VAS, Visual Analogue Scale.

Treatment was discontinued in nine patients (7.1%) because of adverse events. Dosage adjustment was performed in f ve patients (4.0%). Rash was the most frequent single reason for discontinuation ($n = 5$, 4.0%) with all cases developing within 8 weeks of commencing treatment. One patient developed a short-term rash that lasted 10 hours, and was not removed from the study. In all cases the rash resolved completely upon discontinuation of LTG. There was a single serious adverse event. A female patient receiving valproate (800 mg) and LTG (250 mg) was hospitalized due to diplopia and dizziness. These symptoms resolved after LTG discontinuation.

DISCUSSION

Over the past 15–20 years, important advances have been made in the diagnosis and treatment of epilepsy and epileptic syndromes. The recent availability of several new antiepileptic drugs has enhanced the management of patients with epilepsy. Treatment should be initiated with monotherapy and doses slowly escalated to achieve the target level without causing significant adverse effects. If this does not achieve adequate seizure control, further dose increases may be needed. If the treatment is still unsuccessful, monotherapy with an alternative drug should be prescribed[14]. Studies show that monotherapy, either as an initial treatment or as alternative treatment (through an add-on period and consecutive secondary monotherapy), provides adequate control in approximately 70% of adult patients with partial epilepsy[15].

Carbamazepine and valproate remain the first-lin treatments of epilepsy in Poland. We performed an open, multi-centre, prospective trial of LTG in patients with treatment-resistant epilepsy who were receiving monotherapy treatment with carbamazepine or valproate.

Our study demonstrates that LTG is effective in add-on therapy and consecutive monotherapy in adolescents and adults with epilepsy. Over 50% of patients had a reduction in seizure frequency of 50% or more and over 25% were seizure free during LTG monotherapy. These results support and extend the conclusions from previous add-on and withdrawal to LTG monotherapy studies. Brodie reported that 50% of patients experienced at least a 50% reduction in seizure frequency with add-on LTG, and 19% of evaluable patients were seizure free with LTG monotherapy[16].

In the present study, addition of LTG in patients

Table 5: Mean VAS scores in chosen treatment periods.

	Valproate group, $n = 51$ Mean VAS score (CI 95%)	Carbamazepine group $n = 34$ Mean VAS score (CI 95%)
Week 4	4.4 (3.8; 5.0)	5.8 (4.9; 6.6)
Week 12	6.5 (5.9; 7.1)	7.3 (6.7; 7.9)
Week 28	7.9*† (7.5; 8.4)	7.5* (6.7; 8.3)

VAS scores were recorded at the end of the lamotrigine dose escalation phase (week 4), the end of the lamotrigine add-on phase (week 12) and the end of the lamotrigine monotherapy phase (week 28).
* $P < 0.001$ compared to week 4;
† $P < 0.001$ compared to week 12.

receiving valproate monotherapy produced a signifi cantly better response than addition of LTG in patients receiving carbamazepine monotherapy. This findin is also consistent with previous reports[16–18].

The primary aim of AED therapy is to establish a therapeutic dose that provides the best seizure control with minimal side effects. When used in combination as add-on therapy, AEDs can cause a complex array of pharmacokinetic and pharmacodynamic drug interactions, which can easily disturb the established balance and may cause patients to experience an increase in seizures or an increase in drug-related toxicity. Ideally, treatment of epilepsy is achieved with monotherapy. In the present study we have confirme that withdrawal of carbamazepine or valproate can be performed successfully, with over two out of three patients achieving LTG monotherapy, and more than half classifie as responders. A simultaneous increase in VAS scores in both treatment groups also indicates an improved sense of well-being from the perspective of the patient.

The results of this study also indicate that LTG is well tolerated when added to existing AED therapy followed by AED withdrawal. Conversion to LTG monotherapy from a polytherapy regimen with carbamazepine or valproate led to improved tolerance. In the present study the frequency of rash was slightly lower than that previously observed in add-on LTG therapy[19]. All cases were non-serious and occurred during the firs 8 weeks of treatment when patients were receiving add-on therapy and all disappeared, either spontaneously (in one case) or after LTG discontinuation (in f ve cases). In general, the risk of rash increases when the recommended starting dose or the rate of dose escalation are exceeded. The LTG dosage regimen in the current study is consistent with currently recommended guidelines and was strictly adhered to.

Optimizing therapy requires selection of the AED that has been shown to be the most effective for the patient's type of seizures and epileptic syndrome, and that has the most favourable safety profile Some patients require treatment with more than one agent, but alternative monotherapy regimens should be tried firs if the initial AED is ineffective or causes unacceptable side effects[20]. More complex issues concern women of childbearing age. Optimal AED selection in women with epilepsy requires reproductive health issue knowledge, such as contraceptive choice and specifi teratogenic risks[21,22]. The effica y of oral hormonal contraceptives is impaired by concomitant use of liver enzyme-inducing agents such as carbamazepine, phenytoin, barbiturates, and topiramate. Valproate and LTG do not reduce levels of the oral contraceptive hormones and therefore should not increase the risk of their failure[21]. Both carbamazepine and valproate are known to cause neural tube defects (0.5–1.0% and 1–2%, respectively)[23,24]. On the other hand, the animal reproductive toxicology studies are quite favourable for LTG. Although there is no evidence of teratogenicity from pre-clinical studies, the Lamotrigine Pregnancy Registry was established to prospectively collect prenatal LTG exposure and pregnancy outcome data[25].

In summary, this study shows that LTG is an effective AED in add-on therapy and monotherapy and that it is well tolerated. In most cases conversion from adjunctive therapy to LTG monotherapy can be achieved successfully.

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REFERENCES

1. Leach, M. J., Lees, G. and Riddall, D. R. Lamotrigine: mechanisms of action. In: *Antiepileptic Drugs*. 4th Edition (Eds R. H. Levy, R. H. Mattson and B. S. Meldrum, *et al.*). New York, Raven Press, 1995: pp. 861–869.
2. Wang, S. J., Huang, C. C., Hsu, K. S., Tsai, J. J. and Gean, P. W. Inhibition of N-type calcium currents by lamotrigine in rat amygdalar neurones. *Neuroreport* 1996; **7**: 3037–3040.
3. Messenheimer, J., Mullens, E. L., Giorgi, L. and Young, F. Safety review of adult clinical trial experience with lamotrigine. *Drug Safety* 1998; **18**: 281–296.
4. Beran, R. G., Berkovic, S. F., Dunagan, F. M. *et al.* Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalized epilepsy. *Epilepsia* 1998; **39**: 1329–1333.
5. Buchanan, N. The use of lamotrigine in juvenile myoclonic epilepsy. *Seizure* 1996; **5**: 149–151.
6. Messenheimer, J., Ramsay, R. E., Willmore, L. J. *et al.* Lamotrigine therapy for partial seizures: a multicenter placebo-controlled, double-blind, crossover trial. *Epilepsia* 1994; **35**: 113–121.
7. Motte, J., Trevathan, E., Arvidsson, J. F. V. *et al.* Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *New England Journal of Medicine* 1997; **337**: 1807–1812.
8. Schapel, G. J., Beran, R. G., Vajda, F. J. E. *et al.* Double-blind, placebo-controlled crossover study of lamotrigine in treatment-resistant partial seizures. *Journal of Neurology, Neurosurgery and Psychiatry* 1993; **56**: 448–453.
9. Mackay, F. J., Wilton, L. V., Pearce, G. L. *et al.* Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997; **38**: 881–886.
10. Schachter, S. C., Leppik, I. E., Matsuo, F. *et al.* Lamotrigine: a six month, placebo-controlled, safety and tolerance study. *Journal of Epilepsy* 1995; **8**: 201–209.
11. Steiner, T. J., Dellaportas, C. I., Findley, L. J. *et al.* Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia* 1999; **40**: 601–607.
12. Brodie, M. J., Richens, A. and Yuen, A. W. C. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet* 1995; **345**: 476–479.
13. Akyol, A., Yoldas, T., Baydas, G. and Mungen, B. Lamotrigine versus valproate as monotherapy in patients with newly diagnosed epilepsy. *Epilepsia* 1998; **39** (Suppl. 2): S23.
14. Pellock, J. M. Treatment of seizures and epilepsy in children and adolescents. *Neurology* 1998; **51** (Suppl. 4): S8–S14.
15. Mattson, R. H. and Cramer, J. A. The choice of antiepileptic drugs in focal epilepsy. In: *The Treatment of Epilepsy: Principles and Practices* (Ed. E. Wylie). Philadelphia, Lea & Febiger, 1993: pp. 817–823.
16. Brodie, M. J. and Yuen, A. W. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. *Epilepsy Research* 1997; **26**: 423–432.
17. Huber, B., May, Th. and Seidel, M. Lamotrigine in multihandicapped therapy-resistant epileptic patients. *Clinical Drug Investigations* 1998; **16**: 263–277.
18. Risner, M., Messenheimer, J., Giorgi, L., Mullens, L. and Manasco, P. The safety and effica y of Lamictal and valproic acid combination therapy in pediatric epilepsy patients. *Neurology* 1998; **50** (Suppl. 4): A426.
19. Guberman, A. H., Besag, F. M. C., Brodie, M. J. *et al.* Lamotrigine-associated rash: risk/benefi considerations in adults and children. *Epilepsia* 1999; **40**: 985–991.
20. Mattson, R. H. Medical management of epilepsy in adults. *Neurology* 1998; **51** (Suppl. 4): S15–S20.
21. Morrell, M. J. Guidelines for the care of women with epilepsy. *Neurology* 1998; **51** (Suppl. 4): S21–S27.
22. Crawford, P., Appleton, R., Betts, T., Duncan, J., Guthrie, E. and Morrow, J. Best practice guidelines for the management of women with epilepsy. The Women with Epilepsy Guidelines Development Group. *Seizure* 1999; **8**: 201–217.
23. Rosa, F. W. Spina bifid in infants of women treated with carbamazepine during pregnancy. *New England Journal of Medicine* 1991; **324**: 674–677.
24. Omtzigt, J. G. C., Los, F. J., Grobee, D. E. *et al.* The risk of spina bifid aperta after first-trimeste exposure to valproate in a prenatal cohort. *Neurology* 1992; **42** (Suppl. 5): 119–125.
25. Tennis, P and Eldridge, R. Six-year interim results of the Lamotrigine Pregnancy Registry. *Epilepsia* 1999; **40** (Suppl. 2): 196.